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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/415, C07D 405/02 — A1

(11) International Publication Number: WO 97/04772

(43) International Publication Date: 13 February 1997 (13.02.97)

(21) International Application Number: PCT/US96/12581

(22) International Filing Date: 2 August 1996 (02.08.96)

(30) Priority Data:

60/001,792	2 August 1995 (02.08.95)	US
60/010,982	1 February 1996 (01.02.96)	US

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM CORPORATION [US/US]; Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: LUENGO, Juan, Ignacio [ES/US]; 701 Pondview Drive, Audubon, PA 19403 (US). ELLIOTT, John, Duncan [GB/US]; 723 Old Eagle School Road, Wayne, PA 19087 (US).

(74) Agents: HALL, Linda, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).

(81) Designated States: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, IL, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: ENDOTHELIN RECEPTOR ANTAGONISTS

(57) Abstract

Novel pyrroles, pyrazoles and triazoles, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists are described.

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ENDOTHELIN RECEPTOR ANTAGONISTS

FIELD OF INVENTION

The present invention relates to novel pyrroles, pyrazoles and triazoles, pharmaceutical compositions containing these compounds and their use as endothelin receptor antagonists.

Endothelin (ET) is a highly potent vasoconstrictor peptide synthesized and released by the vascular endothelium. Endothelin exists as three isoforms, ET-1, ET-2 and ET-3. [Unless otherwise stated "endothelin" shall mean any or all of the isoforms of endothelin]. Endothelin has profound effects on the cardiovascular system, and in particular, the coronary, renal and cerebral circulation. Elevated or abnormal release of endothelin is associated with smooth muscle contraction which is involved in the pathogenesis of cardiovascular, cerebrovascular, respiratory and renal pathophysiology. Elevated levels of endothelin have been reported in plasma from patients with essential hypertension, acute myocardial infarction, subarachnoid hemorrhage, atherosclerosis, and patients with uraemia undergoing dialysis.

In vivo, endothelin has pronounced effects on blood pressure and cardiac output. An intravenous bolus injection of ET (0.1 to 3 nmol/kg) in rats causes a transient, dose-related depressor response (lasting 0.5 to 2 minutes) followed by a sustained, dose-dependent rise in arterial blood pressure which can remain elevated for 2 to 3 hours following dosing. Doses above 3 nmol/kg in a rat often prove fatal.

Endothelin appears to produce a preferential effect in the renal vascular bed. It produces a marked, long-lasting decrease in renal blood flow, accompanied by a significant decrease in GFR, urine volume, urinary sodium and potassium excretion. Endothelin produces a sustained antinatriuretic effect, despite significant elevations in atrial natriuretic peptide. Endothelin also stimulates plasma renin activity. These findings suggest that ET is involved in the regulation of renal function and is involved in a variety of renal disorders including acute renal failure, cyclosporine nephrotoxicity, radio contrast induced renal failure and chronic renal failure.

Studies have shown that in vivo, the cerebral vasculature is highly sensitive to both the vasodilator and vasoconstrictor effects of endothelin. Therefore, ET may be an important mediator of cerebral vasospasm, a frequent and often fatal consequence of subarachnoid hemorrhage.

ET also exhibits direct central nervous system effects such as severe apnea and ischemic lesions which suggests that ET may contribute to the development of cerebral infarcts and neuronal death.

ET has also been implicated in myocardial ischemia (Nichols et al. Br. J. Pharm. 99: 597-601, 1989 and Clozel and Clozel, Circ. Res., 65: 1193-1200, 1989) coronary vasospasm (Fukuda et al., Eur. J. Pharm. 165: 301-304, 1989 and Lüscher, Circ. 83: 701, 1991) heart failure, proliferation of vascular smooth muscle cells, (Takagi, Biochem & Biophys. Res. Commun.; 168: 537-543, 1990, Bobek et al., Am. J. Physiol. 258:408-C415, 1990) and atherosclerosis, (Nakaki et al., Biochem. & Biophys. Res. Commun. 158: 880-881, 1989, and Lerman et al., New Eng. J. of Med. 325: 997-1001, 1991). Increased levels of endothelin have been shown after coronary balloon angioplasty (Kadel et al., No. 2491 Circ. 82: 627, 1990).

Further, endothelin has been found to be a potent constrictor of isolated mammalian airway tissue including human bronchus (Uchida et al., Eur J. of Pharm. 154: 227-228 1988, LaGente, Clin. Exp. Allergy 20: 343-348, 1990; and Springall et al., Lancet, 337: 697-701, 1991). Endothelin may play a role in the pathogenesis of interstitial pulmonary fibrosis and associated pulmonary hypertension, Glard et al., Third International Conference on Endothelin, 1993, p. 34 and ARDS (Adult Respiratory Distress Syndrome), Sanai et al., Supra, p. 112.

Endothelin has been associated with the induction of hemorrhagic and necrotic damage in the gastric mucosa (Whittle et al., Br. J. Pharm. 95: 1011-1013, 1988); Raynaud's phenomenon, Cinniniello et al., Lancet 337: 114-115, 1991); Crohn's Disease and ulcerative colitis, Munch et al., Lancet, Vol. 339, p. 381; Migraine (Edmeads, Headache, Feb. 1991 p 127); Sepsis (Weitzberg et al., Circ. Shock 33: 222-227, 1991; Pittet et al., Ann. Surg. 213: 262-264, 1991), Cyclosporin-induced renal failure or hypertension (Eur. J. Pharmacol., 180: 191-192, 1990, Kidney Int, 37: 1487-1491, 1990) and endotoxin shock and other

endotoxin induced diseases (Biochem. Biophys. Res. Commun., 161: 1220-1227, 1989, Acta Physiol. Scand. 137: 317-318, 1989) and inflammatory skin diseases. (Clin Res. 41:451 and 484, 1993).

Endothelin has also been implicated in preclampsia of pregnancy. Clark et al., Am. J. Obstet. Gynecol. March 1992, p. 962-968; Kamor et al., N. Eng. J. of Med., Nov 22, 1990, p. 1486-1487; Dekker et al., Eur J. Ob. and Gyn. and Rep. Bio. 40 (1991) 215-220; Schiff et al., Am. J. Ostet. Gynecol. Feb 1992, p. 624-628; diabetes mellitus, Takahashi et al., Diabetologia (1990) 33:306-310; and acute vascular rejection following kidney transplant, Watschinger et al., Transplantation Vol. 52, No. 4, pp. 743-746.

Endothelin stimulates both bone resorption and anabolism and may have a role in the coupling of bone remodeling. Tatrai et al. Endocrinology, Vol. 131, p. 603-607.

Endothelin has been reported to stimulate the transport of sperm in the uterine cavity, Casey et al., J. Clin. Endo and Metabolism, Vol. 74, No. 1, p. 223-225, therefore endothelin antagonists may be useful as male contraceptives. Endothelin modulates the ovarian/menstrual cycle, Kenegsberg, J. of Clin. Endo. and Met., Vol. 74, No. 1, p. 12, and may also play a role in the regulation of penile vascular tone in man, Lau et al., Asia Pacific J. of Pharm., 1991, 6:287-292 and Tejada et al., J. Amer. Physio. Soc. 1991, H1078-H1085. Endothelin also mediates a potent contraction of human prostatic smooth muscle, Langenstroer et al., J. Urology, Vol. 149, p. 495-499.

Thus, endothelin receptor antagonists would offer a unique approach toward the pharmacotherapy of hypertension, acute and chronic renal failure, ischemia induced renal failure, sepsis-endotoxin induced renal failure, prophylaxis and/or treatment of radio-contrast induced renal failure, acute and chronic cyclosporin induced renal failure, cerebrovascular disease, cerebrovascular spasm, subarachnoid hemorrhage, myocardial ischemia, angina, congestive heart failure, acute coronary syndrome, myocardial salvage, unstable angina, asthma, primary pulmonary hypertension, pulmonary hypertension secondary to intrinsic pulmonary disease, atherosclerosis, Raynaud's phenomenon, ulcers, sepsis, migraine, glaucoma,

endotoxin shock, endotoxin induced multiple organ failure or disseminated intravascular coagulation, cyclosporin-induced renal failure and as an adjunct in angioplasty for prevention of restenosis, diabetes, diabetic retinopathy, retinopathy, diabetic nephropathy, diabetic macrovascular disease, atherosclerosis, preclampsia of pregnancy, bone remodeling, kidney transplant, male contraceptives, infertility and priaprism and benign prostatic hypertrophy.

SUMMARY OF THE INVENTION

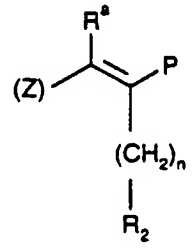
This invention comprises compounds represented by Formula (I) and pharmaceutical compositions containing these compounds, and their use as endothelin receptor antagonists which are useful in the prevention or treatment of a variety of cardiovascular and renal diseases including but not limited to: hypertension, acute and chronic renal failure, cyclosporine induced nephrotoxicity, benign prostatic hypertrophy, pulmonary hypertension, migraine, stroke, subarachnoid hemorrhage, cerebrovascular vasospasm, myocardial ischemia, angina, congestive heart failure, unstable angina, coronary vasospasm and myocardial salvage, the sequelae of diabetes including but not limited to: atherosclerosis, diabetic nephropathy, diabetic retinopathy, retinopathy, diabetic macrovascular disease; and as an adjunct in angioplasty for prevention of restenosis.

This invention further constitutes a method for antagonizing endothelin receptors in an animal, including humans, which comprises administering to an animal in need thereof an effective amount of a compound of Formula (I).

This invention also constitutes intermediates represented by Formula (II). In a further aspect, the present invention provides a process for the preparation of a compound of Formula (I)(d).

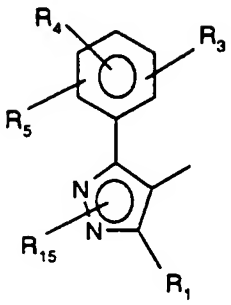
DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are represented by structural Formula (I):

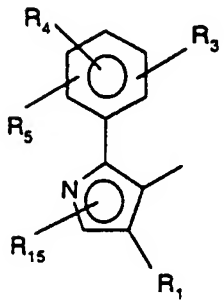


(I)

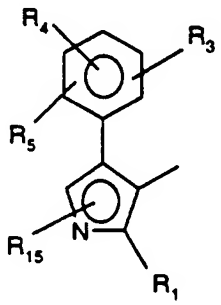
wherein (Z) is



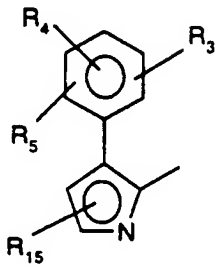
(d)



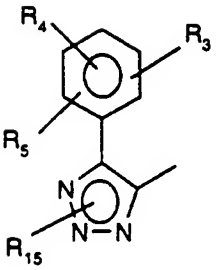
(e)



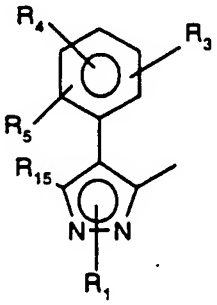
(f)



(g)

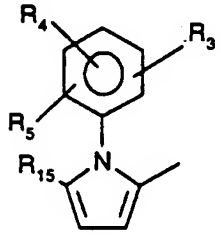


(h)



(i)

or



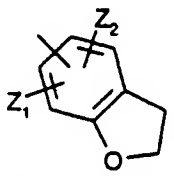
(j)

P is tetrazol-5-yl, CO_2R_6 or $C(O)N(R_6)S(O)_qR_{10}$;

R^a is independently hydrogen or C_{1-6}alkyl;

R_1 is independently hydrogen, Ar, C_{1-6}alkyl or C_{1-6} alkoxy;

R_2 is



;

R_3 and R_5 are independently $R_{13}OH$, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, NO_2, Br, F, I, Cl, CF_3, $NHCOR_6$, $R_{13}CO_2R_7$, -X-R9-Y, $-X(C(R_6)_2)OR_6$, $-(CH_2)_mX'R_8$or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is independently R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl or $NHCOR_6$, wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-8}alkyl;

R_7 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, CO_2R_{12}, halogen or XC_{1-10}alkyl; or R_7 is $(CH_2)_nAr$;

R_8 is independently R_{11}, CO_2R_7, $CO_2C(R_{11})_2O(CO)XR_7$, $PO_3(R_7)_2$, $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$, $CONR_7SO_2R_{11}$, SO_3R_7, SO_2R_7, $P(O)(OR_7)R_7$, CN, $CO_2(CH_2)_mC(O)N(R_6)_2$, $C(R_{11})_2N(R_7)_2$, $C(O)N(R_6)_2$, $NR_7C(O)NR_7SO_2R_{11}$, OR_6, or tetrazole which is substituted or unsubstituted by C_{1-6}alkyl;

R_9 is independently a bond, C_{1-10}alkylene, C_{1-10}alkenylene, C_{1-10}alkylidene, C_{1-10}alkynylene, all of which may be linear or branched, or phenylene, all of which may be unsubstituted or substituted by one of more OH, $N(R_6)_2$, COOH or halogen;

R_{10} is independently C_{1-10}alkyl, $N(R_6)_2$ or Ar;

R_{11} is independently hydrogen, Ar, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH_2OH, $N(R_6)_2$, or halogen;

R_{12} is independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-7}alkynyl;

R_{13} is independently divalent Ar, C_{1-10}alkylene, C_{1-10}alkylidene, C_{2-10}alkenylene, all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

R_{14} is independently hydrogen, C_{1-10}alkyl, XC_{1-10}alkyl, Ar or XAr;

R_{15} is independently hydrogen, Ar, C_{1-6}alkyl, or XAr;

R_{16} is independently C_{1-6}alkyl or phenyl substituted by one or more C_{1-6}alkyl, OH,

C_{1-5}alkoxy, $S(O)_qR_6$, $N(R_6)_2$, Br, F, I, Cl, CF_3 or $NHCOR_6$;

X is independently $(CH_2)_n$, O, NR_6 or $S(O)_q$;

X' is independently O, NR_6 or $S(O)_q$;

Y is independently CH_3 or $X(CH_2)_nAr$;

Ar is:

(a) (b)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more Z_1 or Z_2 groups;

A is independently C=0, or $(C(R_6)_2)_m$;

B is independently $-CH_2-$ or -0-;

Z_1 and Z_2 are independently hydrogen, XR_6, C_{1-8}alkyl, $(CH_2)_qCO_2R_6$, $C(O)N(R_6)_2$, CN, $(CH_2)_nOH$, NO_2, F, Cl, Br, I, $N(R_6)_2$, $NHC(O)R_6$, $O(CH_2)_mC(O)NR_aSO_2R_{16}$, $(CH_2)_mOC(O)NR_aSO_2R_{16}$,

$O(CH_2)_mNR_aC(O)NR_aSO_2R_{16}$ tetrazolyl which may be substituted or unsubstituted by C_{1-6}alkyl, CF_3 or $C(O)R_6$;

m is independently 1 to 3;

n is independently 0 to 6;

q is independently 0, 1 or 2;

provided R_3, R_4 and R_5 are not $O\text{-}O(CH_2)_nAr$ or $O\text{-}OR_6$;

or a pharmaceutically acceptable salt thereof.

All alkyl, alkenyl, alkynyl and alkoxy groups may be straight or branched. Halogen may be Br, Cl, F or I.

The compounds of the present invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active form. All of these compounds and their diastereoisomers are contemplated to be within the scope of the present invention.

Preferred compounds are those wherein:

P is CO_2R_6; more preferably P is CO_2H.

R_1 is hydrogen.

Z_1 and Z_2 are independently hydrogen, CO_2R_6, $(CH_2)_nOH$, C_{1-4}alkyl or C_{1-6} alkoxy, e.g. methoxy.

R_3 and R_5 are independently hydrogen, CO_2R_6, OH, C_{1-8}alkoxy, C_{1-8}alkyl, $N(R_6)_2$, NO_2, Br, F, Cl, I, $R_{13}CO_2R_7$, $X(CH_2)_nR_8$, $(CH_2)mX'R_8$, or $X(C(R_6)_2)_mOR_6$.

In the context of the group R_3 and R_5 preferably do not represent hydrogen. In particular in the group R_3 preferably represents Br, Cl, C_{1-8}alkoxy e.g. methoxy; $X(CH_2)_nR_8$, wherein X preferably represents O, n is 0, 1, or 2, and R_8 is preferably selected from:

CO_2R_6 wherein R_6 is preferably hydrogen;

OR_6 wherein R_6 is preferably H;

tetrazolyl optionally substituted by C_{1-8}alkyl e.g. ethyl;

$CONR_7SO_2R_{11}$ wherein R_7 is H or C_{1-8}alkyl e.g. methyl, R_{11} preferably is

C_{1-8}alkyl (e.g. methyl, isopropyl, or t-butyl) or phenyl optionally substituted by Br, Cl, F, C_{1-8}alkyl e.g. methyl;
or R_8 is phenyl or pyridyl substituted by one or more Br, Cl, CO_2H, CH_2OH; and
R_5 is C_{1-8}alkoxy e.g. methoxy, or $N(R_6)_2$ wherein R_6 preferably is H or methyl.

R_4 is hydrogen, OH, C_{1-5}alkoxy, $N(R_6)_2$, Br, F, Cl, I, $NHCOCH_3$, or $S(O)_q$ C_{1-5}alkyl wherein the C_{1-5}alkyl may be unsubstituted or substituted by OH, methoxy or halogen. R_4 is more preferably hydrogen.

R_6 is hydrogen or C_{1-8}alkyl e.g. methyl and ethyl.

R_7 is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, CO_2R_{12}, halogen, or R_7 is $(CH_2)_nAr$. When R_7 is $(CH_2)_nAr$, n is preferably zero or 1 and Ar is preferably phenyl substituted or unsubstitued by halogen or C_{1-5} alkoxy.

R_{11} is hydrogen, phenyl, pyridyl wherein the phenyl and pyridyl may be substituted or unsubstituted by one or two C_{1-4}alkyl groups; C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH_2OH, $N(R_6)_2$, or halogen;

R_{12} is hydrogen or C_{1-6}alkyl.

R_{13} is phenyl, pyridyl, or C_{2-10}alkylene, all of which may be unsubstituted or substituted by one or more CO_2R_6, OH, CH_2OH, $N(R_6)_2$, or halogen;

R_{15} is preferably hydrogen or C_{1-6}alkyl e.g. ethyl, isopropyl, *n*-butyl, cyclopropylmethyl or cyclopropylethyl.

(Z) is preferably (d).

Preferred compounds are:

(E)-3-[1-*n*-Butyl-5-[2-(2-carboxy-6-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(*E*)-3-[1-*n*-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(E)-3-[1- *n*-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(E)-3-[1- *n*-Butyl-5-[2-(2-carboxy-6-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(E)-3-[1- *n*-Butyl-5-[2-(2-carboxy-5-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

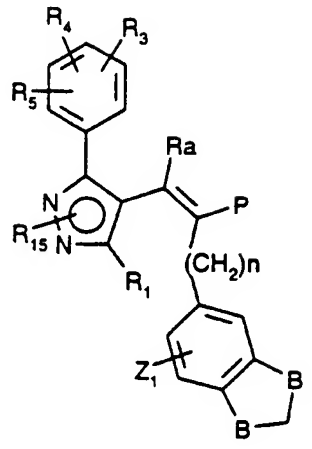
(E)-3-[1- *n*-Butyl-5-[2-(3-carboxy-2-pyridyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-5-yl)methyl]-prop-2-enoic acid;

or

(E)-3-[1- *n*-Butyl-5-[2-(2-carboxy-5-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid.

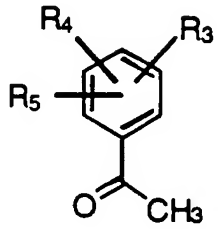
The present invention provides compounds of Formula (I), which may be made by methods similar to those given below.

Compounds of the Formula (Id):



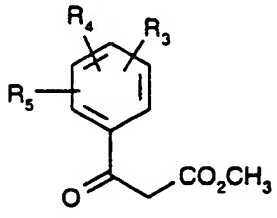
(Id)

wherein one B is CH_2 and the other is O can be prepared by alkylating a ketone of Formula (2):



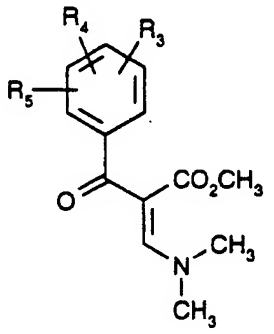
(2)

in dimethyl carbonate in the presence of sodium hydride to provide a b-keto ester of Formula (3).



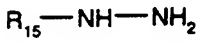
(3)

Condensation of a b-keto ester of Formula (3) with dimethyl formate dimethyl acetal in a suitable solvent such as toluene at approximately 95 °C affords a compound of Formula (4).



(4)

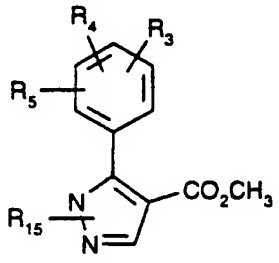
Treatment of a compound of Formula (4) with a hydrazine derivative of the Formula (5)



(5)

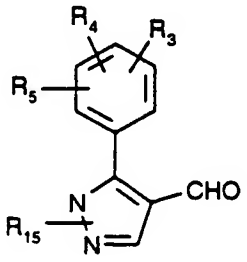
wherein R_{15} is C_{1-6}alkyl;

in suitable solvents such as methanol and water in the presence of sodium acetate provides a pyrazole of Formula (6).



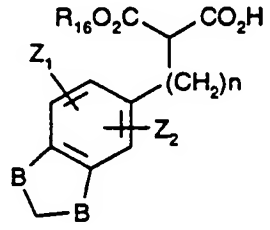
(6)

Reduction of an ester of Formula (6) with a reducing agent such as diisobutylalluminum hydride in a solvent such as dichloromethane followed by oxidation with an oxidant such as Jones reagent in acetone affords an aldehyde of Formula (7).



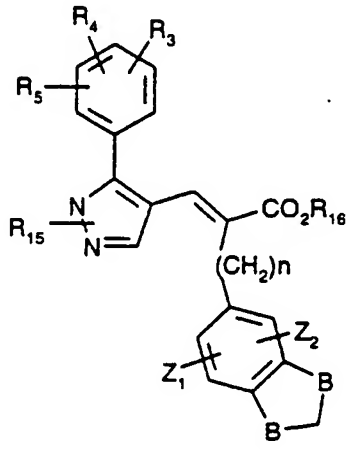
(7)

Knoevenagel condensation of an aldehyde of Formula (7) with a half acid of Formula (8), wherein R_{16} is C_{1-8} alkyl



(8)

in a solvent such as benzene at reflux, in the presence of piperidinium acetate with azeotropic removal of water using a Dean-Stark apparatus to afford an ester of Formula (9).



(9)

Followed if necessary and desired by:

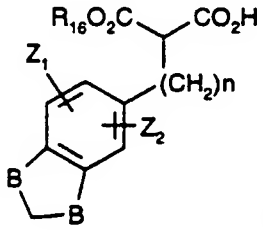
1) deprotection and alkylation and hydrolysis of the R_3, R_4, R_5, R_{15}, R_{16}, Z_1 and Z_2 groups as required and;

2) salt formation

Aldehyde condensation may be effected by heating in the presence of pyridine and acetic acid.

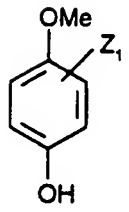
Conversion of an ester of formula (9) into an acid may be carried out using conventional deprotection techniques i.e. hydrolysis.

A half acid of Formula (8),



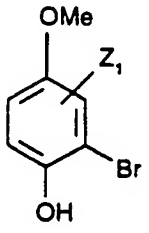
(8)

wherein R_{16} is C_{1-8} alkyl and n is 1, may be prepared starting from 4-methoxyphenol (10)



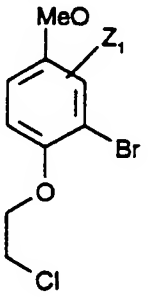
(10)

which upon bromination affords a bromobenzene of Formula (11).



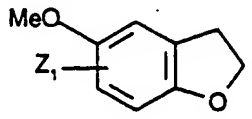
(11)

Alkylation of phenol of Formula (11) with 1,2-dichloroethane under phase transfer reaction conditions provides a compound of Formula (12).



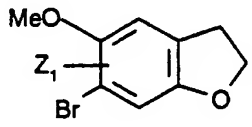
(12)

Treatment of bromobenzene of Formula (12) with an organolithium reagent such n-butyllithium or metal such as magnesium in a solvent such as tetrahydrofuran affords dihydrobenzofuran of Formula (13).



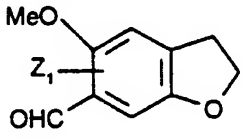
(13)

Bromination of a compound of Formula (13) with hexamethylenetetraamine hydrobromide perbromide in a solvent such as dichloromethane provides bromodihydrobenzofuran of Formula (14).



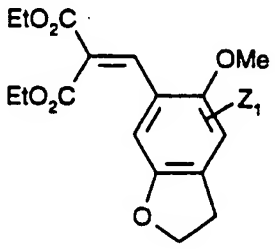
(14)

Metal-halogen exchange of compound of Formula (14) using an organolithium reagent such n-butyllithium in a solvent such as tetrahydrofuran affords an aldehyde of Formula (15).



(15)

Condensation of an aldehyde of Formula (15) with dialkyl malonate such as diethyl malonate in the presence of piperidine and acetic acid in a solvent such as benzene provides an a,b-unsatuated ester of Formula (16).



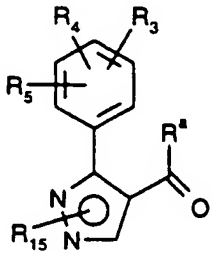
(16)

Treatment of an a,b-unsatuated ester of Formula (16) with sodium borohydride in ethanol followed by mono saponification with aqueous sodium hydroxide in a solvent such as ethanol affords, after acidification with aqueous hydrochloric acid, an acid of Formula (8), whereas R_{16} is ethyl and n is 1.

Other compounds of Formula (Id) may be made by methods well known in the art.

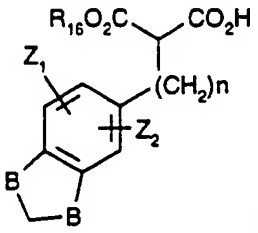
The invention also is a process for preparing compounds of Formula (Id)by:

(a) reaction of a compound of Formula (II)



(II)

or a protected form or precursor thereof (as defined hereinafter) with a compound of Formula (8)



(8)

wherein one B is CH_2 and the other is O, and Z_1, Z_2 and R_{16} are as defined for Formula (Id) hereinabove;

followed if necessary or desired by:

(b) conversion of one compound of Formula (Id) into a different compound of Formula (Id) e.g.

(i) when Formula (Id) contains a group CO_2R_6, CO_2R_7 or CO_2R_{12}, or CO_2R_{16} wherein R_6, R_7, R_{12} or R_{16} is alkyl, conversion to a corresponding compound where R_6, R_7, R_{12} or R_{16} represents hydrogen;

(ii) when Formula (Id) contains hydroxy group (e.g. in R_3, R_4 or R_5) conversion to a different group, e.g. a group $(CH_2)Ar$ where Ar is optionally substituted phenyl, by method well known in the art; and/or

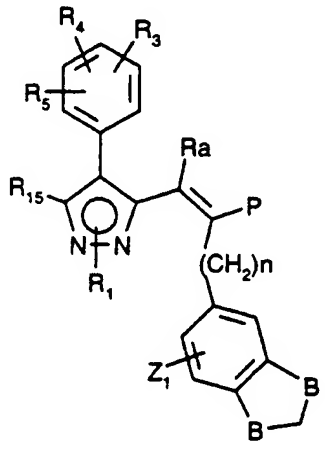
(c) salt formation.

It will be appreciated by those skilled in the art that the substituents R_{15}, R_3, R_4 and R_5 and be introduced at any appropriate stage of the synthesis, preferably at an early stage, using methods well known in the art. In some of the reactions depicted above, particularly those in the early stages of the overall synthesis, one or more of the substitutents R_{15}, R_3, R_4 and R_5 may therefore represent a precursor for the eventual substituent. A precursor for any of the substituents R_{15}, R_3, R_4 and R_5 means a group which may be derivatised or converted into the desired group R_{15},

R_3, R_4 and R_5. It will be further appreciated that it may be necessary or desirable to protect certain of these substituents (or their precursors) at various stages in the reaction sequence. Suitable precursors and protecting groups as well known to those skilled in the art, as are methods for their conversion of removal respectively.

In another aspect the invention provides for an intermediate of the formula (II) wherein R_{15}, R_3, R_4, R_5 and R^a are as described for Formula (I)

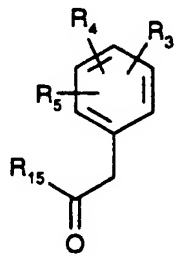
Compounds of Formula (Ii)



(Ii)

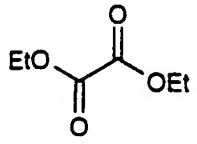
wherein one B is CH2 and the other is O;

can be prepared starting by commercially available ketones of Formula (17)



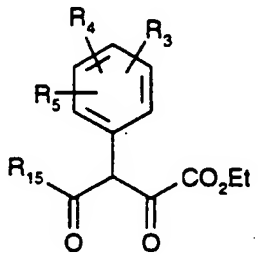
(17)

by reaction with diethyl oxalate of Formula (18)



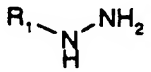
(18)

in the presence of a base such as sodium ethoxide in a solvent such as ethanol to produce a diketone of Formula (19).



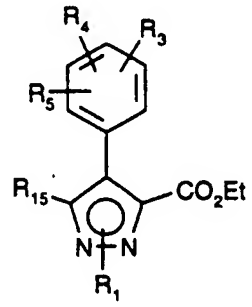
(19)

Reaction of a diketone of Formula (19) with hydrazine derivative of Formula (20)



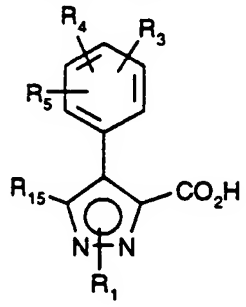
(20)

in a suitable solvent such as ethanol at reflux provides a pyrazole of Formula (21).



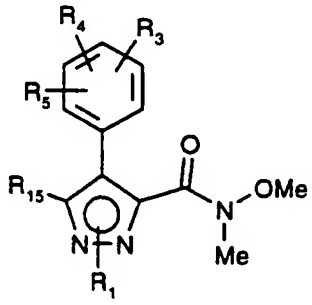
(21)

Saponification of an ester of Formula (21) using lithium hydroxide in a solvent such as aqueous methanol affords, after acidification an acid of the Formula (22),



(22)

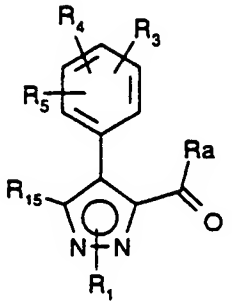
which can be subsequently converted to the corresponding N-methoxy-N-methylamide of Formula (23)



(23)

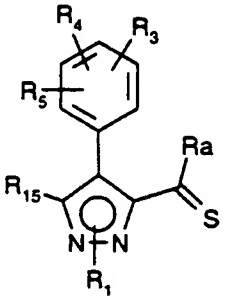
by treatment with methyl chloroformate followed by N,O-dimethylhydroxylamine hydrochloride in the presence of a base such as N-methylpiperidine. Compound of Formula (23) can be treated with an organometallic reagent R^a-M wherein R^a is

C_{1-6} alkyl and M is Li or MgCl; to provide a compound of Formula (24), wherein R^a is C_{1-6}alkyl.



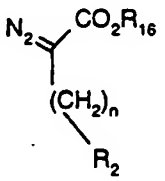
(24)

Alternatively, reaction of compound (24), wherein R^a is C_{1-6}alkyl, with Lawesson's reagent in a suitable solvent such as tetrahydrofuran affords a thione of Formula (25),.



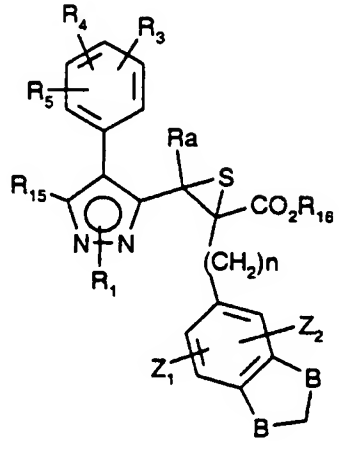
(25)

which can be treated with the diazoester (26)



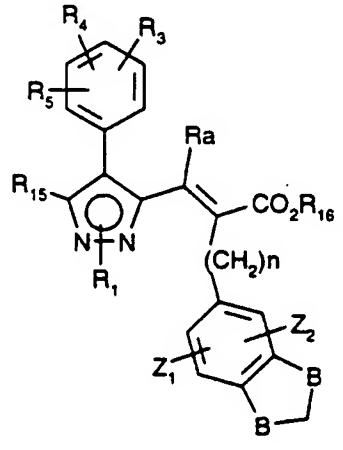
(26)

in refluxing tetrahydrofuran to provide a thiirane of Formula (27).



(27)

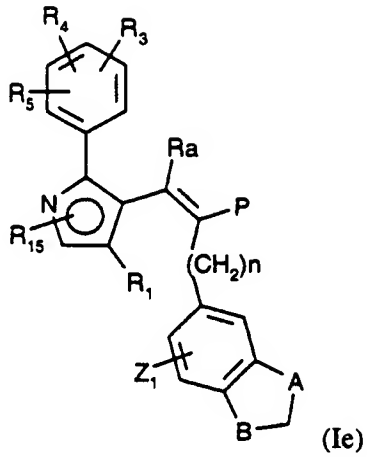
Treatment of a thiirane of Formula (27) with trimethylphosphite at reflux in a solvent such as chloroform provides compounds of Formula (28), wherein R^a is C_{1-6}alkyl.



(28)

Saponification of an ester of Formula (28) using lithium hydroxide in a solvent such as aqueous methanol affords, after acidification with acetic acid, an acid of the Formula (Ii), wherein P is CO_2H.

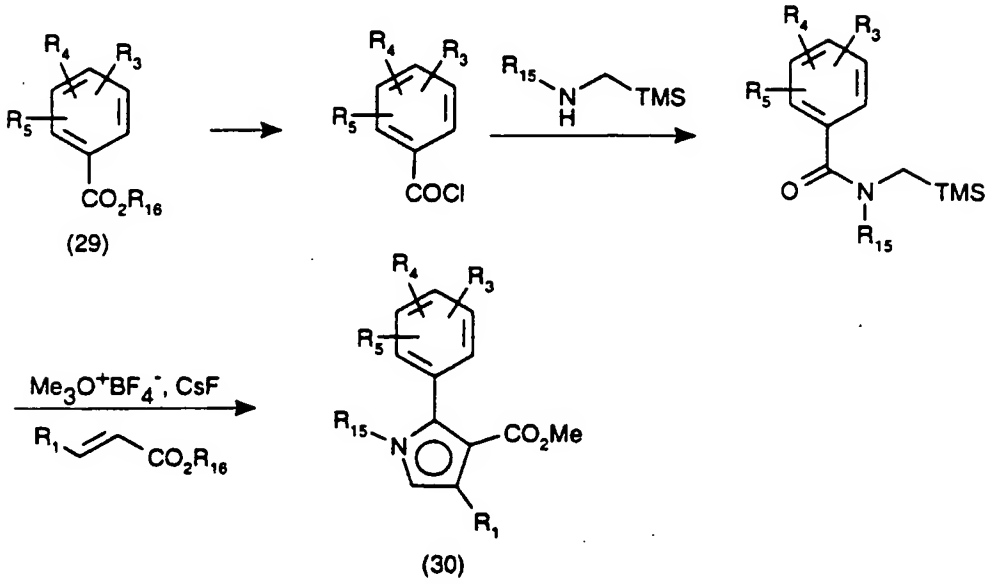
Compounds of the Formula (Ie)



(Ie)

wherein one B is CH_2 and the other is O;

can be prepared following the steps outlined in the following Scheme



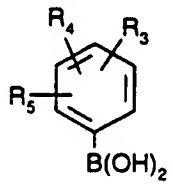
(29)

(30)

starting from an aryl ester of Formula (29), wherein R_{16} is C_{1-8} alkyl, to provide a pyrrole of Formula (30). Compound of Formula (30) can be subsequently converted to compounds of Formula (Ie) following the same sequence of steps as the one

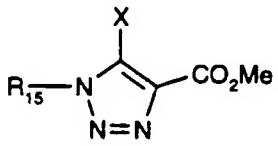
described above for the conversions of compound (6) and compound (21) to compounds (Id) and compound (Ii), respectively.

Compounds of Formula (Ih) may be prepared starting from a boronic acid of Formula (31)



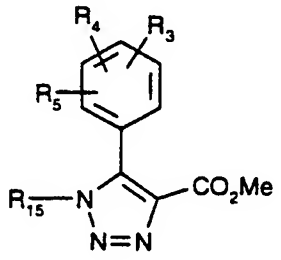
(31)

with a triazole of Formula (32), wherein X is Cr or Br;



(32)

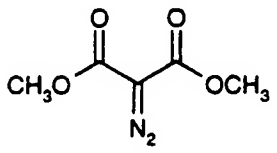
under standard Suzuki coupling conditions to provide an ester of Formula (33)



(33)

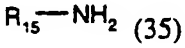
A compound of Formula (31) may be prepared by reaction of a corresponding organometallic derivative (eg lithium or Grignard) with a trialkyl borate followed by hydrolysis.

A compound of Formula (32) may be prepared starting from dimethyl malonate with p-acetaminobenzenesulfonyl azide in a solvent such as acetonitrile in the presence of a base such as triethyl amine to provide dimethyl diazomalonate (34).



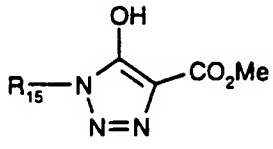
(34)

Treatment of diazomalonate of Formula (34) with an amine of Formula (35)



(35)

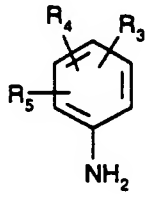
followed by acidic work up provides a triazole of Formula (36)



(36)

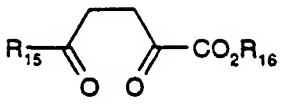
Reaction of a compound of Formula (36) with PX_5, whereas X is Br or Cl, in the presence of potassium carbonate in dimethylformamide affords a compound of Formula (32).

Compounds of Formula (Ij) may be prepared starting from an analine of Formula (37)



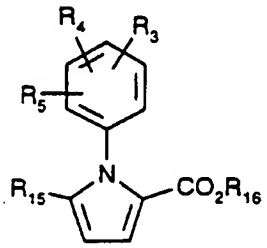
(37)

with a diketone of Formula of (38)



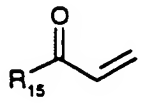
(38)

in a suitable solvent such as ethyl alcohol at reflux to provide a pyrrole of Formula (39).



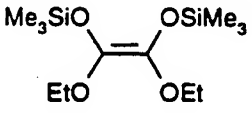
(39)

A diketone of Formula of (38) can be prepared by reacting of a,b-unsatuated ketone of Formula (40)



(40)

with a silyl enol ether of Formula (41)



(41)

in the presence of Lewis acid such as zinc chloride in a suitable solvent such as dichloromethane followed by acidic hydrolysis.

Compounds of Formula (33) and compounds of Formula (39) can be subsequently converted to compounds of Formula (Ih) and compounds of Formula (Ij), respectively, following the same sequence of steps as the one described above for the conversions of compound (6), compound (21) and compound (30) to compounds (Id), compound (Ii) and compound (Ie), respectively.

In order to use a compound of the Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Compounds of Formula (I) and their pharmaceutically acceptable salts may be administered in a standard manner for the treatment of the indicated diseases, for example orally, parenterally, sub-lingually, transdermally, rectally, via inhalation or via buccal administration.

Compounds of Formula (I) and their pharmaceutically acceptable salts which are active when given orally can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, peanut oil, olive oil, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, terra alba, talc, gelatin, agar, pectin, acacia, stearic acid, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a

parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

Typical compositions for inhalation are in the form of a solution, suspension or emulsion that may be administered as a dry powder or in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane.

A typical suppository formulation comprises a compound of Formula (1) or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to themselves a single dose.

Each dosage unit for oral administration contains suitably from 0.1 mg to 500 mg/Kg, and preferably from 1 mg to 100 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 100 mg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. Each dosage unit for intranasal administration contains suitably 1-400 mg and preferably 10 to 200 mg per person. A topical formulation contains suitably 0.01 to 1.0% of a compound of Formula (I).

The daily dosage regimen for oral administration is suitably about 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for parenteral administration is suitably about 0.001 mg/Kg to 40 mg/Kg, of a compound of the Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free acid. The daily dosage regimen for intranasal administration and oral inhalation is suitably about 10 to about 500 mg/person. The active

ingredient may be administered from 1 to 6 times a day, sufficient to exhibit the desired activity.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

The biological activity of the compounds of Formula (I) are demonstrated by the following tests:

I. Binding Assay

A) CHO cell membrane preparation.

CHO cells stably transfected with human ET_A and ET_B receptors were grown in 245 mm x 245 mm tissue culture plates in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum. The confluent cells were washed with Dulbecco's phosphate-buffered saline containing a protease inhibitor cocktail (5 mM EDTA, 0.5 mM PMSF, 5 ug/ml of leupeptin and 0.1 U/ml of aprotinin) and scraped in the same buffer. After centrifugation at 800 *x g*, the cells were lysed by freezing in liquid nitrogen and thawing on ice followed by homogenization (30 times using a glass dounce homogenizer) in lysis buffer containing 20 mM Tris HCl, pH 7.5, and the protease inhibitor cocktail. After an initial centrifugation at 800 x *g* for 10 min to remove unbroken cells and nuclei, the supernatants were centrifuged at 40,000 *x g* for 15 min and the pellet was resuspended in 50 mM Tris HCl, pH 7.5, and 10 mM $MgCl_2$ and stored in small aliquots at -70°C after freezing in liquid N_2. Protein was determined by using the BCA method and BSA as the standard.

(B) Binding studies.

[^{125}I]ET-1 binding to membranes prepared from CHO cells was performed following the procedure of Elshourbagy *et al.* (1993). Briefly, the assay was initiated in a 100 ul volume by adding 25 ul of [^{125}I]ET-1 (0.2-0.3 nM) in 0.05% BSA to membranes in the absence (total binding) or presence (nonspecific binding) of 100 nM unlabeled ET-1. The concentrations of membrane proteins were 0.5 and 0.05 ug per assay tube for ET_A and ET_B receptors, respectively. The incubations (30°C, 60 min) were stopped by dilution with cold buffer (20 mM Tris

HCl, pH 7.6, and 10 mM $MgCl_2$) and filtering through Whatman GF/C filters (Clifton, NJ) presoaked in 0.1% BSA. The filters were washed 3 times (5 ml each time) with the same buffer by using a Brandel cell harvester and were counted by using a gamma counter at 75% efficiency.

The following examples are illustrative and are not limiting of the compounds of this invention.

EXAMPLE 1

(E)-3-[1-*n*-Butyl-5-[2-(2-carboxy-6-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

a) 2-Bromo-4-methoxyphenol

To a solution of 4-methoxyphenol (13.00 g, 104.84 mmol) in DMF (50 mL) was added bromine (5.40 mL, 104.84 mmol) at 0 °C. The reaction was allowed to warm to room temperature. After stirring for 2 h the reaction was quenched with water and extracted with ethyl acetate (3x200 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 21.28 g of the crude title compound as a dark oil: ^1H NMR (250 MHz, $CDCl_3$) d 7.49 (b, 1H), 6.96 (d, 1H), 6.72-6.62 (m, 2H), 3.71 (s, 3H).

b) 2-Bromo-1-(2-chloroethoxy)-4-methoxybenzene

To a solution of 2-bromo-4-methoxyphenol (20.00 g, 98.04 mmol) in 1,2-dichloroethane (50.00 mL, 0.63 mol) was added sodium hydroxide (12.00 g, 0.29 mol) and benzyltriethylammonium chloride (3.00 g) in water (150 mL). The mixture was stirred at reflux for 24 h and extracted with ethyl acetate (3x150 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash chromatography (1:1 diethyl ether/hexane) of

the residue gave 14.20 g (66% over two steps) of the title compound as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) d 7.09 (d, 1H), 6.82-6.72 (m, 2H), 4.27 (t, 2H), 3.75 (t, 3H), 3.71 (s, 3H).

c) 5-Methoxy-2,3-dihydrobenzofuran

To a solution of 2-bromo-1-(2-chloroethoxy)-4-methoxybenzene (1.38 g, 5.22 mmol) in THF was added 190 mg (7.82 mmol) of Mg and MeI (3 mL). The mixture was sonicated for 2 h and stirred at room temperature for additional 20 h. The reaction was quenched with 3N HCl (50 mL) and extracted with 1:1 hexane/ethyl acetate (3x50 mL). The combined organic extracts were washed with saturated $NaHCO_3$ brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash chromatography (3:1 hexane/ethyl acetate) of the residue gave 0.66 g (85%) of the title compound as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) d 6.80 (d, 1H), 6.70 (d, 1H), 6.65 (dd, 1H), 4.53 (t, 2H), 3.75 (s, 3H), 3.18 (t, 3H).

d) 6-Bromo-5-methoxy-2,3-dihydrobenzofuran

To a solution of 5-methoxy-2,3-dihydrobenzofuran (1.00 g, 6.66 mmol) in dichloromethane (10 mL) was added hexamethylenetetraamine hydrobromide perbromide (2.79g, 7.32 mmol) at -78 ^{o}C. The reaction was allowed to warm to room temperature. After stirring for 3 h, the reaction was quenched with water and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 1.45 g (96%) of the title compound as a dark solid: ^{1}H NMR (250 MHz, $CDCl_3$) d 7.00 (s, 1H), 6.82 (s, 1H), 4.57 (t, 2H), 3.81 (s, 3H), 3.15 (t, 2H).

e) 5-Methoxy-2,3-dihydrobenzofuran-6-al

To a solution of 6-bromo-5-methoxy-2,3-dihydrobenzofuran (9.20 g, 40.35 mmol) in THF (50 mL) was dropwise added *n*-Butyl lithium (24.00 mL, 38.40 mmol) at

-78 °C. After stirring for 30 min, DMF (5.00 mL, 60.53 mmol) was added and the mixture was allowed to stir at room temperature for 2 h. The reaction was quenched with water and extracted with ethyl acetate (3x150 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Flash chromatography (1:1 ether/hexane) of the residue afforded 5.42g (76%) of the title compound as a yellow solid: ^{1}H NMR (250 MHz, $CDCl_3$) d 10.32 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 4.57 (t, 2H), 3.91 (s, 3H), 3.25 (t, 2H).

f) Diethyl 2-(5-methoxy-2,3-dihydrobenzofuran-6-yliden)-malonate

To a solution of 5-Methoxy-2,3-dihydrobenzofuran-6-al (295 mg, 1.66 mmol) in benzene was added diethyl malonate (265 mg, 1.66 mmol), acetic acid (20 mL, 0.35 mmol) and piperidine (30 mL, 0.30 mmol). The mixture was heated at reflux for 3 h and then poured into 100 mL of water. This mixture was extracted with three 50 mL portion of ethyl acetate. The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave quatitative yield of the title compound as a yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) d 8.02 (s, 1H), 6.79 (s, 1H), 6.78 (s, 1H), 4.52 (t, 2H), 4.30 (m, 4H), 3.80 (s, 3H), 3.18 (t, 2H), 1.28 (m, 6H).

g) Diethyl 2-(5-methoxy-2,3-dihydrobenzofuranyl)methyl-malonate

To a solution of diethyl 2-(5-methoxy-2,3-dihydrobenzofuran-6-yliden)-malonate (1.80 g, 5.62 mmol) in ethanol (25 mL) was added sodium borohydride (0.22 g, 5.66 mmol) at room temperature. After stirring for 2 h the reaction was quenched with water and extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash chromatography (1:1 diethyl ether/hexane) of the dark residue afforded 1.47 g (82%) of the title compound as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) d 6.70 (s, 1H), 6.54 (s, 1H), 4.44 (t, 2H), 4.12 (q, 2H), 3.74 (m, 4H), 3.11 (m, 4H), 1.18 (t, 6H).

h) Ethyl, hydrogen 2-(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl-malonate

To a solution of diethyl 2-(5-methoxy-2,3-dihydrobenzofuranyl)methyl-malonate (6.55 g, 20.34 mmol) in ethanol (50 mL) was added a solution of potassium hydroxide (1.35 g, 24.40 mmol) in water (10 mL). The reaction mixture was stirred at room temperatur for 5 h. After concentrating the aqueous layer was washed with ether and acidified with concentrated HCl to pH 1 and extracted with ethyl acetate (3x100 mL). The organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 5.26 g (88%) of the title compound as a white solid: ^{1}H NMR (250 MHz, $CDCl_3$) d 11.43 (b, 1H), 6.72 (s, 1H), 6.58 (s, 1H), 4.48 (t, 2H), 4.16 (q, 2H), 3.82 (t, 1H), 3.75 (s, 3H), 3.14 (t, 3H),1.20 (t, 3H); MS (ESI) m/e 295.2 $[M+H]^+$; m.p.: 114- 116 ^oC.

i) 4-Chloro-2-hydroxyacetophenone

In a 500 mL of round bottom flask purged with argon was placed 26.00 g (0.153 mol) of 3-acetoxychlorobenzene, cooled with ice bath. Then 30.00 g (0.225 mol) of $AlCl_3$ was added in portions. The resulting mixture was heated to 140 oC for 2 h (caution: vigorous evolution of gas) and then cooled to 0oC, treated with 15 mL of conc. HCl in 100 mL of ice water, extracted with EtOAc (3x300 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent gave 24.00 g (92%) of the title compound as a light yellow liquid: ^{1}H NMR (250 MHz, $CDCl_3$) d 10.7 (s, 1H), 7.65 (d, *J*=8.6 Hz, 1H), 6.98 (d, *J*=1.8 Hz, 1H), 6.87 (dd, *J*=1.8, 8.6 Hz, 1H), 2.61 (s, 3H).

j) 4-Chloro-2-methoxymethoxyacetophenone

To a solution of 4-chloro-2-hydroxyacetophenone (22.00 g, 0.129 mol) in DMF (200 mL) was added K_2CO_3 (72.00 g, 0.516 mol) and bromomethylmethyl ether (0.134 mol). After stirring at 55 ^oC for 1 h, the mixture was poured into water and extracted

with EtOAc (3x300 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4) and removal of the solvent under reduced pressure gave 25.00 g (90%) of the title compound as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) d 7.68 (d, *J*=8.3 Hz, 1H), 7.22 (d, *J*=1.8 Hz, 1H), 7.00 (dd, *J*=1.8, 8.3 Hz, 1H), 5.28 (s, 2H), 3.53 (s, 3H), 2.62 (s, 3H).

k) Methyl 2-(4-chloro-2-methoxymethoxy)benzoylacetate

To a solution of 4-Chloro-2-methoxymethoxyacetophenone (25.00 g, 0.116 mol) in dimethyl carbonate (150 mL) was added 7.5 g of 80% NaH (0.257 mol). After stirring for 10 min. at room temperature, the mixture was heated to 70 °C for 45 min. The resulting mixture was allowed to cool to room temperature and partitioned between water and ethyl acetate. The organic layer was separated and washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 29.00 g (92%) of the title compound as an oil: MS (ESI) *m/z* 273 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.82 (d, *J*=8.4 Hz, 1H), 7.25 (d, *J*=1.8 Hz, 1H), 7.06 (dd, *J*=1.8, 8.4 Hz, 1H), 5.25 (s, 2H), 3.97 (s, 2H), 3.72 (s, 3H), 3.51 (s, 3H).

l) Methyl (Z)-2-(4-chloro-2-methoxymethoxy)benzoyl-3-(dimethylamino)propenoate

A mixture of Methyl 2-(4-chloro-2-methoxymethoxy)benzoylacetate (24.00 g, 0.107 mol) and *N,N*-dimethylformamide dimethyl acetal (25.51 g, 0.214 mol) was heated to 90 °C overnight. Concentration under reduced pressure gave 34.86 g (100%) of the title compound as an oil: MS (ESI) *m/z* 328 $(M+H)^+$; ^{1}H NMR (400 MHz, $CDCl_3$) d 7.71 (s,1H), 7.25 (d, 1H), 7.13 (s,1H), 7.00 (d, 1H), 5.12 (s, 2H), 3.46 (s, 6H), 3.44 (s, 6H).

m) Methyl 1-*n*-butyl-5-(4-chloro-2-methoxymethoxyphenyl)-1H-pyrazol-4-yl carboxylate

To a mixture of Methyl (Z)-2-(4-chloro-2-methoxymethoxy)benzoyl-3-(dimethylamino)propenoate (34.00 g, 0.104 mol) and *n*-butylhydrazine (37.00 g, 0.208 mol) in 600 mL of MeOH/H_2O (9:1) was added NaOAc (84.86 g, 0.624 mol). The resulting mixture was stirred at room temperature overnight and then partitioned between water and CH_2Cl_2. The organic layer was separated and washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 35.50 g (97%) of the title compound as an oil: MS (ESI) *m/z* 353 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) d 7.93 (s,1H), 7.04-7.22 (m, 3H), 5.01 (dd, *J*=6.8, 9.5 Hz, 2H), 3.75-3.92 (m, 2H), 3.60 (s, 3H), 3.30 (s, 3H), 1.65 (m, 2H), 1.12 (m, 2H), 0.74 (t, 3H).

n) 1-*n*-Butyl-5-(4-chloro-2-methoxymethoxyphenyl)-4-hydroxymethylpyrazole

To a solution of Methyl 1-*n*-butyl-5-(4-chloro-2-methoxymethoxyphenyl)-1H-pyrazol-4-yl carboxylate (10.00 g, 0.028 mol) in 200 mL of CH_2Cl_2 at 0 °C was added 85.2 mL of 1.5 M Dibal-H in toluene. After stirring for 1 h, the reaction was quenched with MeOH (100 mL) followed by addition of 35 mL of conc. HCl in 200 mL of water. The resulting mixture was stirred for 15 min. and extracted with CH_2Cl_2 (3x200 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 9.50 g (97%) of the title compound as a oil: MS (ESI) *m/z* 325 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) d 7.63 (s,1H), 7.13-7.29 (m,3H), 5.09 (s, 2H), 4.36 (dd, 2H), 3.80-3.98 (m,2H), 3.35 (s, 3H), 1.70 (m, 2H), 1.18 (m, 2H), 0.81 (t, 3H).

o) 1-*n*-Butyl-5-(4-chloro-2-methoxymethoxyphenyl)-1H-pyrazol-4-yl carboxaldehyde

To a solution of 1-*n*-Butyl-5-(4-chloro-2-methoxymethoxyphenyl)-4-hydroxymethylpyrazole (10.00 g, 30.86 mmol) in 150 mL of acetone at 0 °C was

added of Jones' reagent until pink color persisted (30 mL). 60 mL of isopropyl alcohol was then added and the resulting mixture was stirred at room temperature for 15 min, diluted with 300 mL of cold water, extracted with CH_2Cl_2 (3x200 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash column chromatography of the residue with 25% EtOAc in hexane gave 5.50 g (56%) of the title compound as an oil: MS (ESI) *m/z* 323 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) d 9.54 (s,1H), 8.07 (s, 1H), 7.35 (d, 1H), 7.18 (m, 2H), 5.13 (s, 2H), 3.90-4.05 (m, 2H), 3.38 (s, 3H), 1.75 (m, 2H), 1.20 (m, 2H), 0.83 (t, 3H).

p) Ethyl (*E*)-3-[1-*n*-butyl-5-(4-chloro-2-methoxymethoxyphenyl)-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate

To a mixture of 1-*n*-Butyl-5-(4-chloro-2-methoxymethoxyphenyl)-1*H*-pyrazol-4-yl carboxaldehyde (5.50 g, 17.08 mmol) and Ethyl, hydrogen 2-(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl-malonate (7.28 g, 24.70 mmol) in 50 mL of benzene was added piperidine (2.16 g, 25.41 mmol) and AcOH (0.51 g, 8.50 mmol), respectively. After heating at reflux for 3 h, the mixture was poured into water, extracted with EtOAc (3x100 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash column chromatography of the residue with 25% EtOAc in hexane gave 4.50 g (48%) of the title compound as an oil: MS (ESI) *m/z* 555 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) d 7.53 (s,1H), 7.37 (s, 1H), 7.32 (s, 1H), 7.13 (m, 2H), 6.78 (s, 1H), 6.45 (s, 1H), 5.11 (s, 2H), 4.47 (t, 2H), 4.14 (m, 2H), 3.89 (m, 2H), 3.85 (s, 3H), 3.38 (s, 3H), 3.16 (t, 2H), 1.65 (m, 2H), 1.20 (t, 3H), 1.17 (m, 2H), 0.79 (t, 3H).

q) Ethyl (*E*)-3-[1-*n*-butyl-5-(4-chloro-2-hydroxyphenyl)-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate

To a solution of Ethyl (*E*)-3-[1-*n*-butyl-5-(4-chloro-2-methoxymethoxyphenyl)-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate

(4.50 g, 8.10 mmol) in EtOH (60 mL) was added 0.6 mL of conc. HCl. After heating at reflux for 3 h, the mixture was concentrated and then diluted with EtOAc. The resulting mixture was washed with 5% $NaHCO_3$, brine and dried (Na_2SO_4). After removing the solvent, column chromatography of the residue with 25% EtOAc in hexane gave 2.65 g (64%) of the title compound as a solid: m.p. 158-160 °C; MS (ESI) *m/z* 511 $(M+H)^+$; ^1H NMR (400 MHz, $CDCl_3$) d 7.58 (s,1H), 7.47 (s, 1H), 7.02 (d, 1H), 6.78 (s, 1H), 6.62 (dd, 1H), 6.59 (d, 1H), 6.48 (s, 2H), 5.50 (bs, 1H), 4.48 (t, 2H), 4.12 (m, 2H), 3.85-3.95 (m, 4H), 3.83 (s, 3H), 3.81 (s, 3H), 3.16 (t, 2H), 1.67 (m, 2H), 1.20 (t, 3H), 1.17 (m, 2H), 0.80 (t, 3H).

r) Methyl 3-chloro-2-methylbenzoate

To a solution of 3-chloro-2-methylbenzoic acid (1.00 g, 5.86 mmol) in methanol (25 mL) was added 3 drops of sulfuric acid. The mixture was stirred at reflux for 18 h. After concentrating the residue was dissolved in ether, washed with 10% sodium hydroxide solution, brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave 0.95 g (88%) of the title compound as a white solid: ^1H NMR (250 MHz, $CDCl_3$) d 7.62 (d, 1H), 7.41 (d, 1H), 7.05 (t, 1H), 3.82 (s, 3H), 2.55 (s, 3H).

s) 2-Chloro-6-methyl carboxylate benzylbromide

To a solution of methyl 3-chloro-2-methylbenzoate (1.30 g, 7.04 mmol) in benzene (20 mL) was added NBS (1.50 g, 8.45 mmol) and benzoyl peroxide (0.20 g, 0.83 mmol). After stirring at reflux for 18 h, the mixture was poured into water, and the resulting mixture was extracted with ethyl acetate (3x50 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash column chromatography (1:1 ether/hexane) of the residue gave 1.87 g (82%) of the title compound as a dark oil: ^1H NMR (250 MHz, $CDCl_3$) d 7.72 (d, 1H), 7.55 (d, 1H), 7.21 (t, 1H), 5.09 (s, 2H), 3.92 (s, 3H).

t) Ethyl (*E*)-[1-*n*-butyl-5-[2-(2-methoxycarbonyl)phenylmethoxy-4-chloro-phenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate

To a solution of the ethyl (*E*)-[1-*n*-butyl-5-(2-hydroxy-4-chlorophenyl)-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate (0.20 g, 0.39 mmol) and methyl 2-bromomethyl-3-chlorobenzoate (0.13 g, 0.47 mmol) in DMF (5 mL) was added sodium hydride (0.02 g, 0.59 mmol) at 0 °C. The mixture was stirred at room temperature for 4 h. After an aqueous work up, extracting with ethyl acetate (3 x 15 mL), the combined organic extracts were washed with brine and dried (Na_2SO_4). After removing the solvent under reduced pressure, flash column chromatography (1:1 ethyl acetate/hexane) of the residue afforded the title compound as an oil (0.22 g, 80%). ^{1}H NMR (250 MHz, $CDCl_3$) d 7.78 (d, 1H), 7.55 (d, 1H), 7.48 (s, 1H), 7.32 (m, 2H), 7.12 (d, 2H), 6.75 (s, 1H), 6.45 (s, 1H), 5.55 (dd, *J*= 10, 27.5 Hz, 2H),4.49 (t, 2H), 4.10 (q, 2H), 3.83 (s, 3H) 3.77 (t, 2H), 3.65 (s, 3H), 3.15 (t, 2H), 1.52 (quintet, 2H), 1.20 (t, 3H), 1.05 (sextet, 2H), 0.75 (t, 3H).

u) (*E*)-3-[1-*n*-Butyl-5-[2-(2-carboxy-6-chlorophenyl)methoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-propen-2-oic acid

To a solution of the ethyl (*E*)-[1-*n*-butyl-5-[2-[2-(methoxycarbonyl)-6-chlorophenylmethoxy]-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate (0.20 g, 0.29 mmol) in methanol (5 mL) was added a solution of sodium hydroxide (0.04 g, 0.87 mmol) in water (2 mL). The mixture was stirred at reflux for 18 h. The methanol was removed under reduced pressure and the aqueous layer was washed with ether. The aqueous layer was then acidified with concentrated HCl to pH 1 and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with water, brine and dried (Na_2SO_4). Removal of the solvent gave a solid. Recrystallization from methanol yielded the title compound as a light yellow solid (0.17 g, 91%): ^{1}H NMR (400 MHz $CDCl_3$) d 7.75 (d, 1H), 7.80 (s, 1H), 7.48 (m, 2H), 7.33 (s, 1H), 7.25 (t, 1H), 7.10 (s, 1H), 7.05 (m, 2H), 6.65 (s, 1H), 6.35 (s, 1H), 5.49 (dd, *J*=10, 27.5 Hz, 2H),

4.40 (t, 2H), 3.79 (m, 5H) 3.63 (t, 2H), 3.05 (t, 2H), 1.50 (quintet, 1H), 1.30 (quintet, 1H), 0.94 (quintet, 2H), 0.60 (t, 3H); MS(ESI) m/e 652.2 $[M+H]^+$; mp: 155-157 °C (methanol); Anal. ($C_{34}H_{32}Cl_2N_2O_7$) calcd: C, 62.62; H, 4.96; N, 4.30. found: C, 62.40; H, 5.32; N, 4.19.

EXAMPLE 2

(*E*)-3-[1-*n*-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

a) Ethyl (*E*)-3-[1-*n*-Butyl-5-[2-(2-methoxycarbonyl)phenylmethoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate

Following the procedure of Example (1t) except substituting methyl 2-bromomethylbenzoate for methyl 2-bromomethyl-3-chlorobenzoate, the title compound was prepared in 85% yield.

b) Following the procedure of Example (1u) except substituting Ethyl (*E*)-3-[1-*n*-Butyl-5-[2-(2-methoxycarbonyl)phenylmethoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate for ethyl (*E*)-[1-*n*-butyl-5-[2-[2-(methoxycarbonyl)-6-chlorophenylmethoxy]-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-2-propenoate, the title compound was prepared in 90% yield as a white solid: R_f 0.58 (1:1 EtOAc/hexane with 1% AcOH); ^1H NMR (400 MHz $CDCl_3$) d 8.19 (d, 1H), 7.58 (s, 1H), 7.53 (s, 1H), 7.49 (t, 1H), 7.30 (m, 2H), 7.13 (m, 3H), 6.77 (s, 1H), 6.48 (s, 1H), 5.52 (bs, 2H), 4.45 (t, 2H), 3.92 (m, 2H) 3.82 (s, 3H), 3.80 (bs, 2H), 3.12 (t, 2H), 1.65 (m, 2H), 1.12 (m, 2H), 0.76 (t, 3H); MS(ESI) m/e 618 $[M+H]^+$; mp: 116-118°C. Anal. ($C_{34}H_{33}ClN_2O_7.0.5H_2O$) calcd: C, 65.22; H, 5.47; N, 4.47. found: C, 65.03; H, 5.33; N, 4.37.

EXAMPLE 3

(E)-3-[1- *n*-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(dihydrobenzofuran-5-yl)methyl]-prop-2-enoic acid

98-99°C

EXAMPLE 4

(E)-3-[1- *n*-Butyl-5-[2-(2-Carboxyphenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(6-methoxy-2,3-dihydrobenzofuran-5-yl)methyl]-prop-2-enoic acid

104-106°C

EXAMPLE 5

(E)-3-[1- *n*-Butyl-5-[2-(2-Carboxyphenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

198-200°C

EXAMPLE 6

(E)-3-[1- *n*-Butyl-5-[2-(2-Carboxy-6-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

EXAMPLE 7

(E)-3-[1- *n*-Butyl-5-[2-(2-Carboxy-5-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

122-124°C

EXAMPLE 8

(E)-3-[1- *n*-Butyl-5-[2-(2-Carboxy-4-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

120-122°C

EXAMPLE 9

(E)-3-[1- *n*-Butyl-5-[2-(3-carboxy-2-pyridyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-5-yl)methyl]-prop-2-enoic acid

EXAMPLE 10

(E)-3-[1- *n*-Butyl-5-[2-(cyclopentyloxy)-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

156-158°C

EXAMPLE 11

(E)-3-[1- *n*-Butyl-5-[2-(N,N-diethylamido)methoxy-4-methoxyphenyl)-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

178-180°C

EXAMPLE 12

(E)-3-[1- *n*-Butyl-5-[2-(5-tetrazolyl)methoxy]-4-methoxyphenyl-1H-pyrazol-4-yl]-2-(5-methoxy-2,3-dihydrobenzofuran-6-yl)-methyl]-prop-2-enoic acid

128-130°C

EXAMPLE 13

(E)-3-[1- *n*-Butyl-5-[2-(2-picolyl)oxy-4-methoxy]phenyl-1H-pyrazol-4-yl]-2-(5-methoxy-2,3-dihydrobenzofuran-6-yl)-methyl]-prop-2-enoic acid

132-135°C

EXAMPLE 14

(E)-3-[1- *n*-Butyl-5-[2-(2-Carboxy-5-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

110-112°C

EXAMPLE 15

(E)-3-[1- *n*-Butyl-5-[2-(4-methoxyphenoxy)-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid

91-92°C

EXAMPLE 16

(E)-3-[1- *n*-Butyl-5-[2-N-ethyl-5-tetrazolyl)methoxy]-4-methoxyphenyl-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrofuran-6-yl)methyl]-prop-2-enoic acid

EXAMPLE 17

(E)-3-[1-*n*-Butyl-5-[1-N-ethyl-5-tetrazolyl)methoxy]-4-methoxyphenyl-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrofuran-6-yl)methyl]-prop-2-enoic acid

EXAMPLE 18

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

Inhalant Formulation

A compound of Formula I, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

Tablets/Ingredients		Per Tablet
1.	Active ingredient (Cpd of Form. I)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg
		2.3 mg

Procedure for tablets:

Step 1 Blend ingredients No. 1, No. 2, No. 3 and No. 4 in a suitable mixer/blender.

Step 2 Add sufficient water portion-wise to the blend from Step 1 with careful mixing after each addition. Such additions of water and mixing until the mass is of a consistency to permit its conversion to wet granules.

Step 3 The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen.

Step 4 The wet granules are then dried in an oven at 140°F (60°C) until dry.

Step 5 The dry granules are lubricated with ingredient No. 5.

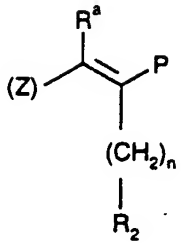
Step 6 The lubricated granules are compressed on a suitable tablet press.

Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of formula I in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then steriled by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

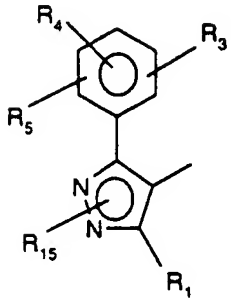
CLAIMS:

1. A compound of Formula (I):

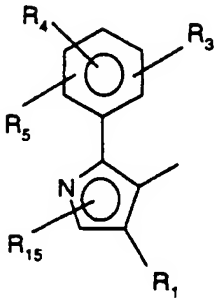


(I)

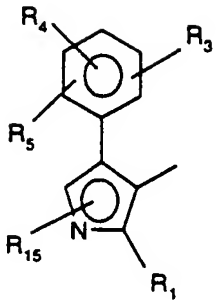
wherein (Z) is



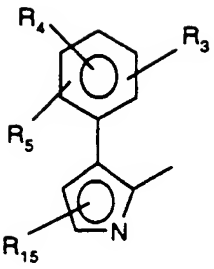
(d)



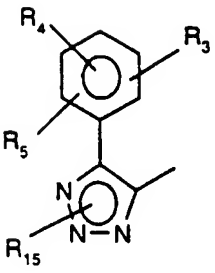
(e)



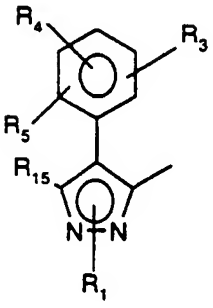
(f)



(g)

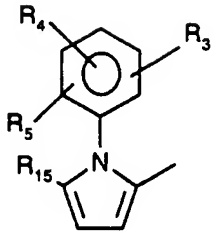


(h)



(i)

or



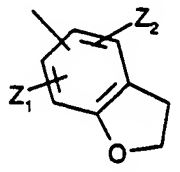
(j)

P is tetrazol-5-yl, CO_2R_6 or $C(O)N(R_6)S(O)_qR_{10}$;

R^a is independently hydrogen or C_{1-6}alkyl;

R_1 is independently hydrogen, Ar, C_{1-6}alkyl or C_{1-6} alkoxy;

R_2 is



;

R_3 and R_5 are independently $R_{13}OH$, C_{1-8}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, NO_2, Br, F, I, Cl, CF_3, $NHCOR_6$, $R_{13}CO_2R_7$, -X-R_9-Y, $-X(C(R_6)_2)OR_6$, $-(CH_2)_mX'R_8$or $-X(CH_2)_nR_8$ wherein each methylene group within $-X(CH_2)_nR_8$ may be unsubstituted or substituted by one or two $-(CH_2)_nAr$ groups;

R_4 is independently R_{11}, OH, C_{1-5}alkoxy, $S(O)_qR_{11}$, $N(R_6)_2$, Br, F, I, Cl or $NHCOR_6$, wherein the C_{1-5}alkoxy may be unsubstituted or substituted by OH, methoxy or halogen;

R_6 is independently hydrogen or C_{1-8}alkyl;

R_7 is independently hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, CO_2R_{12}, halogen or XC_{1-10}alkyl; or R_7 is $(CH_2)_nAr$;

R_8 is independently R_{11}, CO_2R_7, $CO_2C(R_{11})_2O(CO)XR_7$, $PO_3(R_7)_2$, $SO_2NR_7R_{11}$, $NR_7SO_2R_{11}$, $CONR_7SO_2R_{11}$, SO_3R_7, SO_2R_7, $P(O)(OR_7)R_7$, CN, $CO_2(CH_2)_mC(O)N(R_6)_2$, $C(R_{11})_2N(R_7)_2$, $C(O)N(R_6)_2$, $NR_7C(O)NR_7SO_2R_{11}$, OR_6, or tetrazole which is substituted or unsubstituted by C_{1-6}alkyl;

R_9 is independently a bond, C_{1-10}alkylene, C_{1-10}alkenylene, C_{1-10}alkylidene, C_{1-10}alkynylene, all of which may be linear or branched, or phenylene, all of which may be unsubstituted or substituted by one of more OH, $N(R_6)_2$, COOH or halogen;

R_{10} is independently C_{1-10}alkyl, $N(R_6)_2$ or Ar;

R_{11} is independently hydrogen, Ar, C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH_2OH, $N(R_6)_2$, or halogen;

R_{12} is independently hydrogen, C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-7}alkynyl;

R_{13} is independently divalent Ar, C_{1-10}alkylene, C_{1-10}alkylidene, C_{2-10}alkenylene, all of which may be unsubstituted or substituted by one or more OH, CH_2OH, $N(R_6)_2$ or halogen;

R_{14} is independently hydrogen, C_{1-10}alkyl, XC_{1-10}alkyl, Ar or XAr;

R_{15} is independently hydrogen, Ar, C_{1-6}alkyl, or XAr;

R_{16} is independently C_{1-6}alkyl or phenyl substituted by one or more C_{1-6}alkyl, OH,

C_{1-5}alkoxy, $S(O)_qR_6$, $N(R_6)_2$, Br, F, I, Cl, CF_3 or $NHCOR_6$;

X is independently $(CH_2)_n$, O, NR_6 or $S(O)_q$;

X' is independently O, NR_6 or $S(O)_q$;

Y is independently CH_3 or $X(CH_2)_nAr$;

Ar is:

(a) (b)

naphthyl, indolyl, pyridyl, thienyl, oxazolidinyl, thiazolyl, isothiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, thiadiazolyl, morpholinyl, piperidinyl, piperazinyl, pyrrolyl, or pyrimidyl; all of which may be unsubstituted or substituted by one or more Z_1 or Z_2 groups;

A is independently C=0, or $(C(R_6)_2)_m$;

B is independently $-CH_2-$ or -0-;

Z_1 and Z_2 are independently hydrogen, XR_6, C_{1-8}alkyl, $(CH_2)_qCO_2R_6$, $C(O)N(R_6)_2$, CN, $(CH_2)_nOH$, NO_2, F, Cl, Br, I, $N(R_6)_2$, $NHC(O)R_6$, $O(CH_2)_mC(O)NR_aSO_2R_{16}$, $(CH_2)_mOC(O)NR_aSO_2R_{16}$,

$O(CH_2)_mNR_aC(O)NR_aSO_2R_{16}$ tetrazolyl which may be substituted or unsubstituted by C_{1-6}alkyl, CF_3 or $C(O)R_6$;

m is independently 1 to 3;

n is independently 0 to 6;

q is independently 0, 1 or 2;

provided R_3, R_4 and R_5 are not $O\text{-}O(CH_2)_nAr$ or $O\text{-}OR_6$;

or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I) wherein P is CO_2R_6; R_1 is hydrogen; R_3 and R_5 are independently hydrogen, CO_2R_6, OH, C_{1-8}alkoxy, C_{1-8}alkyl, $N(R_6)_2$, NO_2, Br, F, Cl, I, $R_{13}CO_2R_7$, $X(CH_2)_nR_8$, $(CH_2)mX'R_8$, or $X(C(R_6)_2)_mOR_6$; R_4 is hydrogen, OH, C_{1-5}alkoxy, $N(R_6)_2$, Br, F, Cl, I, $NHCOCH_3$, or $S(O)_q$ C_{1-5}alkyl wherein the C_{1-5}alkyl may be unsubstituted or substituted by OH, methoxy or halogen; R_6 is hydrogen, methyl or ethyl; R_7 is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, CO_2R_{12}, halogen, or R_7 is $(CH_2)_nAr$ wherein n is zero or 1 and Ar is substituted phenyl; R_{11} is hydrogen, phenyl, pyridyl all of which may be substituted or unsubstituted by one or two C_{1-4}alkyl groups; C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH_2OH, $N(R_6)_2$, or halogen; R_{12} is hydrogen or C_{1-6}alkyl; R_{13} is phenyl, pyridyl, or C_{2-10}alkylene, all of which may be unsubstituted or substituted by one or more CO_2R_6, OH, CH_2OH, $N(R_6)_2$, or halogen; R_{15} is hydrogen or C_{1-6}alkyl; and (Z) is (d).

3. A compound of claim 2 wherein P is CO_2H; R_1 is hydrogen; Z_1 and Z_2 are independently hydrogen, CO_2R_6, $(CH_2)_nOH$, C_{1-4}alkyl or C_{1-6} alkoxy; R_3 is Br, Cl, C_{1-8}alkoxy or $X(CH_2)_nR_8$, wherein X is O, n is 0, 1, or 2, and R_8 is selected from: CO_2H, OH, tetrazolyl optionally substituted by C_{1-8}alkyl; $CONR_7SO_2R_{11}$ wherein R_7 is H or C_{1-8}alkyl, R_{11} is C_{1-8}alkyl or phenyl optionally substituted by Br, Cl, F, C_{1-8}alkyl; or R_8 is phenyl or pyridyl substituted

by one or more Br, Cl, CO_2H, CH_2OH; R_5 is methoxy or $N(R_6)_2$ wherein R_6 is H or methyl; R_4 is hydrogen; R_6 is hydrogen, methyl or ethyl; R_7 is hydrogen, C_{1-10}alkyl, C_{2-10}alkenyl or C_{2-8}alkynyl, all of which may be unsubstituted or substituted by one or more OH, $N(R_6)_2$, CO_2R_{12}, halogen, or R_7 is $(CH_2)_nAr$ wherein R_7 is $(CH_2)_nAr$ and n is preferably zero or 1 and Ar is preferably phenyl substituted or unsubstituted by halogen or C_{1-5} alkoxy; R_{11} is hydrogen, phenyl, pyridyl all of which may be substituted or unsubstituted by one or two C_{1-4}alkyl groups; C_{1-8}alkyl, C_{2-8}alkenyl, C_{2-8}alkynyl, all of which may be substituted or unsubstituted by one or more OH, CH_2OH, $N(R_6)_2$, or halogen; R_{12} is hydrogen or C_{1-6}alkyl; R_{13} is phenyl, pyridyl, or C_{2-10}alkylene, all of which may be unsubstituted or substituted by one or more CO_2R_6, OH, CH_2OH, $N(R_6)_2$, or halogen; R_{15} is hydrogen, ethyl, isopropyl, *n*-butyl, cyclopropylmethyl or cyclopropylethyl; and (Z) is (d).

4. A compound of claim 1 selected from :

(E)-[1-*n*-Butyl-5-[2-(2-carboxy-6-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(*E*)-3-[1-*n*-Butyl-5-[2-(2-carboxyphenyl)methoxy-4-chlorophenyl]-1*H*-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoate;

(E)-[1- *n*-Butyl-5-[2-(2-Carboxyphenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(E)-[1- *n*-Butyl-5-[2-(2-Carboxy-6-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl] -prop-2-enoic acid;

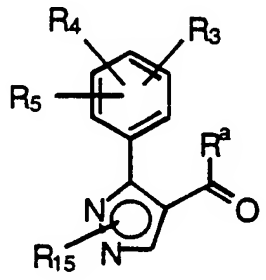
(E)-[1- *n*-Butyl-5-[2-(2-Carboxy-5-chlorophenyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid;

(E)-[1- *n*-Butyl-5-[2-(3-carboxy-2-pyridyl)methoxy-4-methoxyphenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-5-yl)methyl]-prop-2-enoic acid; or

(E)-[1- *n*-Butyl-5-[2-(2-Carboxy-5-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid.

5. A compound of Claim 1 which is (E)-3-[1-*n*-Butyl-5-[2-(2-carboxy-6-chlorophenyl)methoxy-4-chlorophenyl]-1H-pyrazol-4-yl]-2-[(5-methoxy-2,3-dihydrobenzofuran-6-yl)methyl]-prop-2-enoic acid.

6. A compound of Formula (II):



(II)

wherein R^a, R_3, R_4, R_5 and R_{15} are as described in claim 1 for Formula (I).

7. A pharmaceutical composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

8. A compound of claim 1 for use as an endothelin receptor antagonist.

9. A method of treatment of diseases caused by an excess of endothelin comprising administering to a subject in need thereof, an effective amount of an endothelin receptor antagonist of Claim 1.

10. A method of treating hypertension, renal failure or cerebrovascular disease which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

11. A method for the treatment of chronic renal failure which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

12. A method of treatment of benign prostatic hypertrophy which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

13. A method of treatment of congestive heart failure which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

14. A method of treatment of unstable angina, coronary vasospasm and myocardial salvage. which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

15. A method of preventing or treating restenosis which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

16. A method of treatment of pulmonary hypertension which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

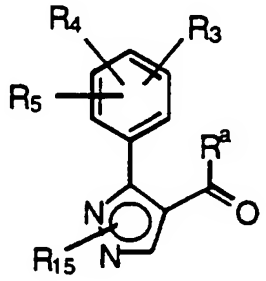
17. A method of treatment of atherosclerosis which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

18. A method of preventing and treating the sequelae of diabetes which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

19. A method of treatment of stroke or subarachnoid hemorrhage which comprises administering to a subject in need thereof, an effective amount of a compound of Claim 1.

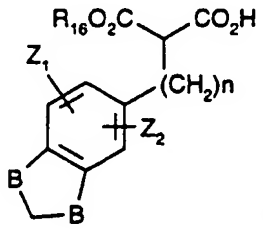
20. A process for preparing a compound of Formula (I)(d) by:

(a) Reaction of a compound of Formula (II)



(II)

or a protected form or precursor thereof with a compound of Formula (8)



(8)

wherein one B is CH_2 and the other is O, and R_2 and R_{16} are as defined in claim 1 for Formula (Id);

followed if necessary or desired by:

(b) conversion of one compound of Formula (Id) into a different compound of Formula (Id) e.g.

(i) when Formula (Id) contains a group CO_2R_6, CO_2R_7 or CO_2R_{12} wherein R_6, R_7 or R_{12} is alkyl, conversion to a corresponding compound where R_6, R_7 or R_{12} represents hydrogen;

(ii) when Formula (Id) contains a hydroxy group (e.g. in R_3, R_4 or R_5) conversion to a different group, e.g. a group $(CH_2)Ar$ where Ar is optionally substituted phenyl, by a method well known in the art; and/or

(c) salt formation.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12581

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/415; C07D 405/02
US CL :514/406; 548/364.4
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/406; 548/364.4

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ON LINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 4,965,282 A (TAKAMURA et al.) 23 October 1990, see column 1, lines 8-16.	4, 5
A	US, 3,703,513 A (YAMAMOTO et al.) 21 November 1972, see column 1, line 16 to column 2, line 16.	4, 5

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 OCTOBER 1996	27 NOV 1996
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer R. W. RAMSUER TCJ Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/12581

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-3, 6-20
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Please See Extra Sheet.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte..ational application No.
PCT/US96/12581

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

The multitude of variables and their permutations and combinations (e.g. Z, P, R1, through R16, Ar, X, X1Y, A, B, Z1, Z2, etc. and the provisos) result in claimed subject matter that is so broad in scope that it is so broad in scope that it is rendered virtually incomprehensible and thus no meaningful search can be given. Note also that the claimed subject matter lacks a significant structural element qualifying as the special technical feature that clearly defines a contribution over the prior art. The subject matter claimed contains a vinylene group which does not define a contribution over the prior art. Therefore the first discernable invention as found in claim 4 (and the method of treating renal failure therewith) has been searched.